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MECHANISMS OF SEIZURE SUSCEPTIBILITY AND EPILEPTOGENESIS

Fever, febrile seizures, and epileptogenesis

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SUMMARY

Febrile seizures (FS) are common and are associated with increased probability of temporal lobe epilepsy (TLE). However, whether FS can provoke TLE in the nonpredisposed brain is unknown. Using an immature rat model, we established that long FS cause TLE, and that duration of FS governed the severity of epilepsy. Epileptogenesis was accompanied, perhaps causally, by ion channel dysfunction and inflammatory changes. Because FS are a prevalent antecedent of TLE, studying the epileptogene-

sis that follows them provides powerful insight and potential therapies for epilepsy. For an expanded treatment of this topic see *Jasper's Basic Mechanisms of the Epilepsies, Fourth Edition* (Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AC, eds) published by Oxford University Press (available on the National Library of Medicine Bookshelf [NCBI] at www.ncbi.nlm.nih.gov/books).

KEY WORDS: Epilepsy, Hyperpolarization-activated cyclic-nucleotide gated (HCN) channels, Hyperthermia, Inflammation, Neuron-restrictive silencer factor, Rodent model.

Febrile seizures (FS) occur in one of 20–50 children, and when long or complex, are statistically associated with increased probability of developing temporal lobe epilepsy (TLE). However, it is unclear if FS can directly cause epilepsy, or if TLE takes place only in the presence of cortical dysplasia, ion channel mutation, or other predisposing factors. We created a model of FS in immature rodents using hyperthermia, where fever cannot be induced (Toth et al., 1998; Dubé et al., 2007). In this model, we established that FS by themselves cause TLE, and that the severity of the resulting seizures is a function of the duration of the inciting FS (Dubé et al., 2010).

Searching for the mechanisms of FS-induced epileptogenesis, we found long-lasting change in the expression of hyperpolarization-activated cyclic-nucleotide gated (HCN) channels, and specifically an early and persistent reduction of HCN1 isoform, which was associated with major alteration of the properties of the current conducted by these channels, I_h . The repression of HCN1 was governed by the neuron-restrictive silencer factor NRSF, and was associated with repression of several hundred additional genes, essentially reprogramming normal hippocampal neurons and rendering them hyperexcitable.

Augmented cytokine expression was found in brains that became epileptic after FS, and the potential involvement of inflammation in the cascade of molecular events that culminates in NRSF-mediated corruption of normal developmental gene programs after FS is discussed.

Because FS are the most common antecedent of TLE, understanding and predicting epileptogenesis that follows them is crucial. Our studies indicate that cortical dysplasia or ion channel mutations are not required for the development of TLE after prolonged FS. In addition, studies to date suggest that magnetic resonance imaging (MRI) might provide an early and selective biomarker for epileptogenesis or cognitive deficits provoked by FS, providing a crucial tool for potential preventive interventions.

DISCLOSURE

The authors declare no conflicts of interest.

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